Macular Edema

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Member of Advisory Boards:
Alcon, Alimera, Allergan, Astellas, Bayer, GeneSignal, GSK, Novartis, Pfizer

Macular Edema

1. Definition – Classification
2. Frequency – Morbidity (DR, VO)
3. DR Clinical Evaluation – Macular Edema as complication
4. Biomarkers of Progression
5. Pathogenesis
6. Treatment of Macular Edema

1. Definition / Classification

Non specific sign of ocular disease

Wide variety of situations:

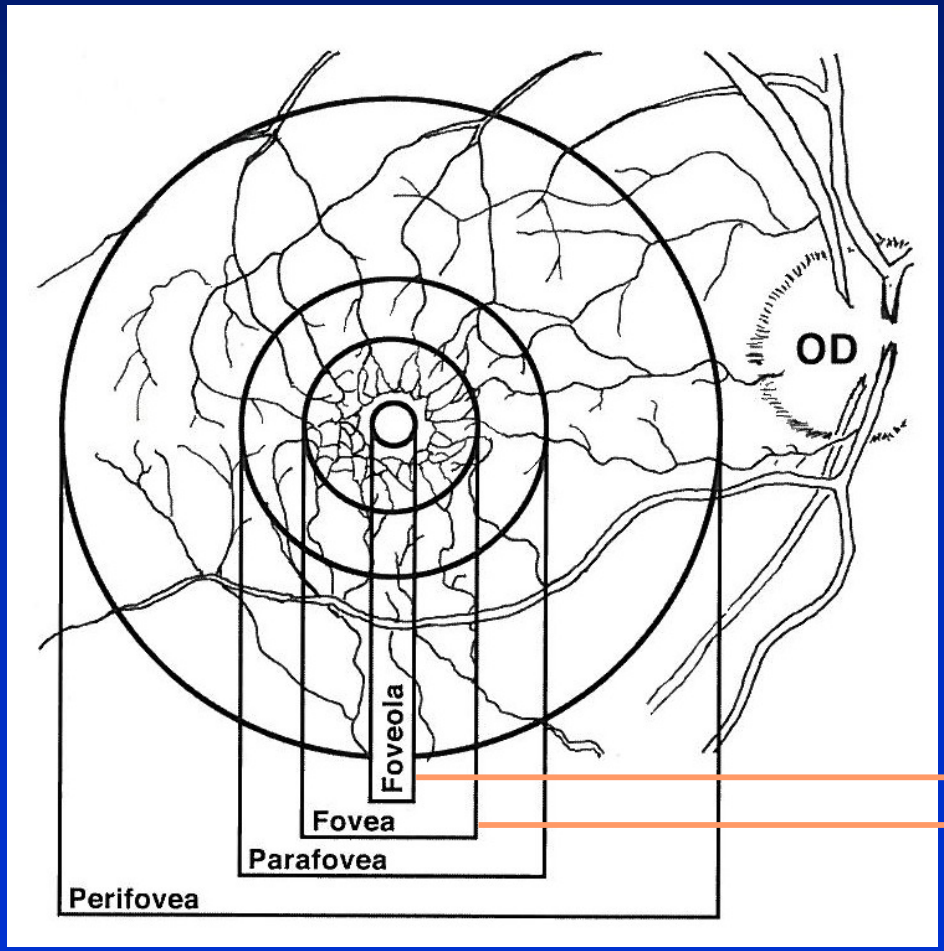
Diabetes, venous occlusions, trauma, uveitis, surgery, age-related macular degeneration, etc.

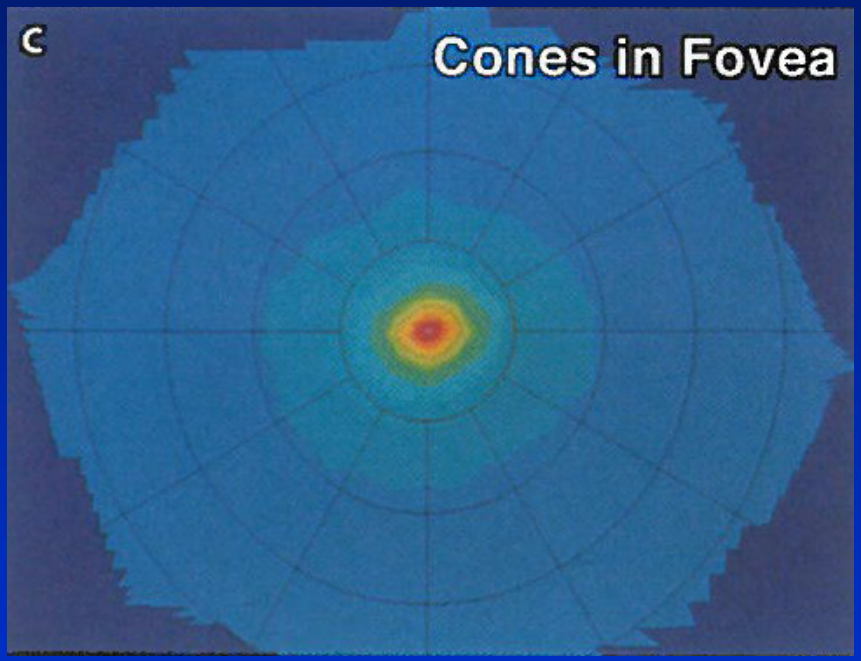
<u>Retinal Edema = Increased thickening of the retina</u>

Intracelullar

Extracelullar – due to a breakdown of the Blood-Retinal Barrier

Fovea - Macula





300µ

1000µ

Clinically Significant Macular Edema (ETDRS)

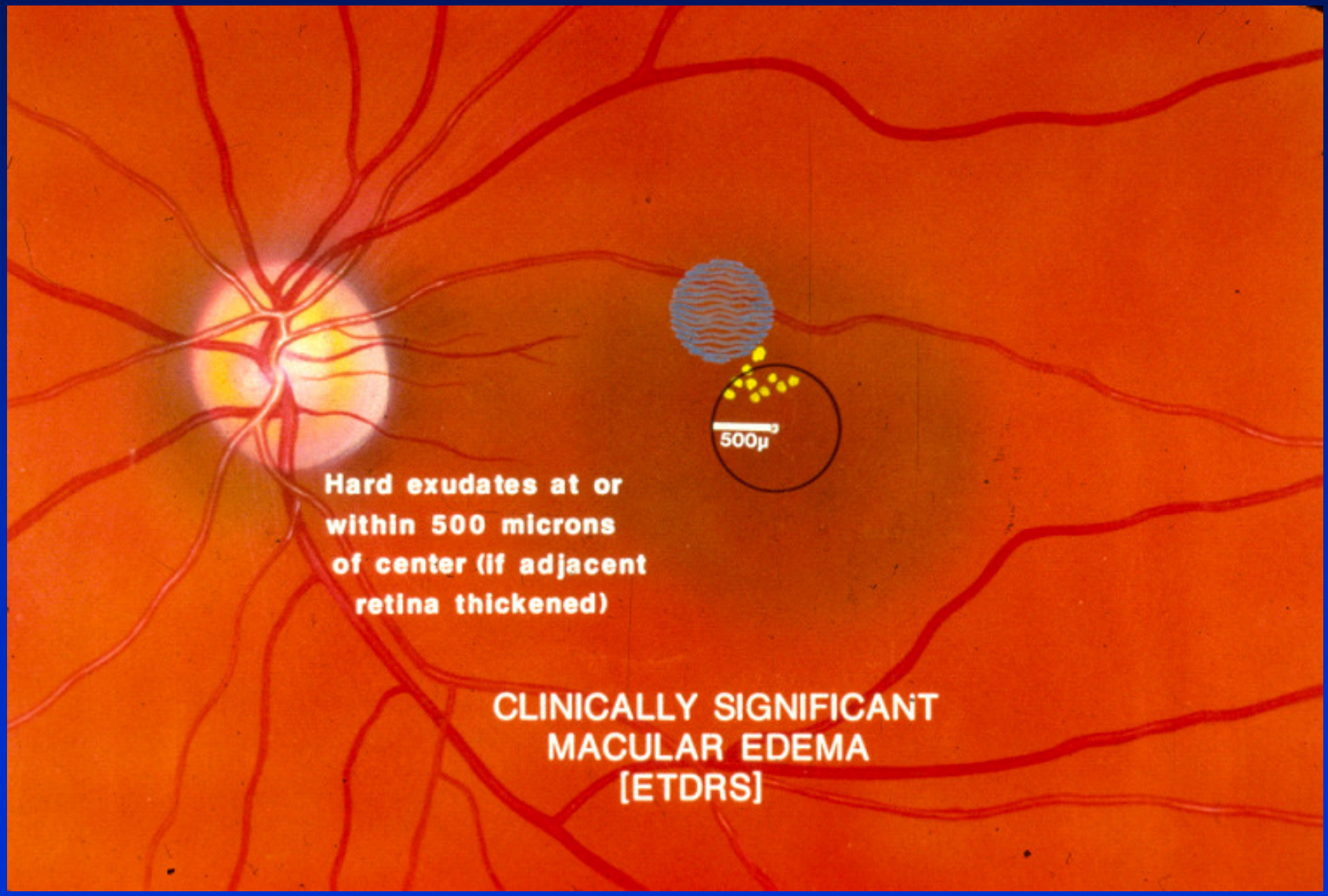
Relevance for Visual Acuity - **Location**

1. thickening of the retina at or within 500 μm of the center of the macula;

2. hard exudates at or within 500 μm of the center of the macula (if associate with thickening of the adjacent retina);

3. zone(s) of retinal thickening of 1 DD or larger, any part of which is within 1 DD of the center of the macula.

Clinically Significant Macular Edema



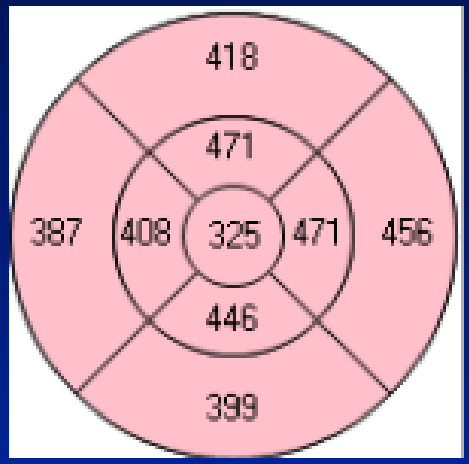
Clinical Evaluation of DME

Replaced by objective measurements

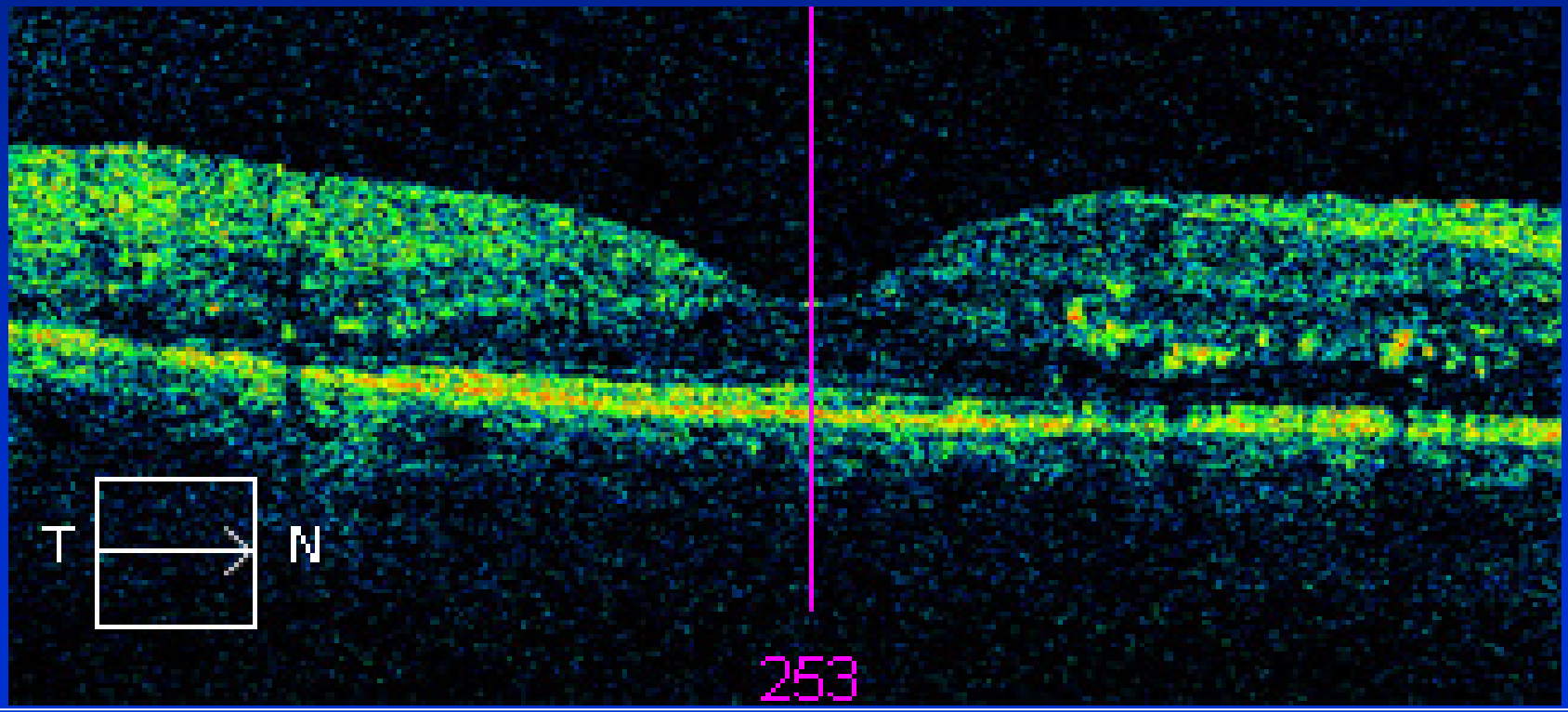
Subjective	Objective
Ophthalmoscopy	OCT
Slit-lamp	
Stereo photography	

Essential – Location of edema vs. fovea

Amount of Edema



	Central Subfield Thickness (µm)	Cube Volume (mm^3)	Cube Average Thickness (µm)
ILM - RPE	325	14.7	409



Location vs. Fovea

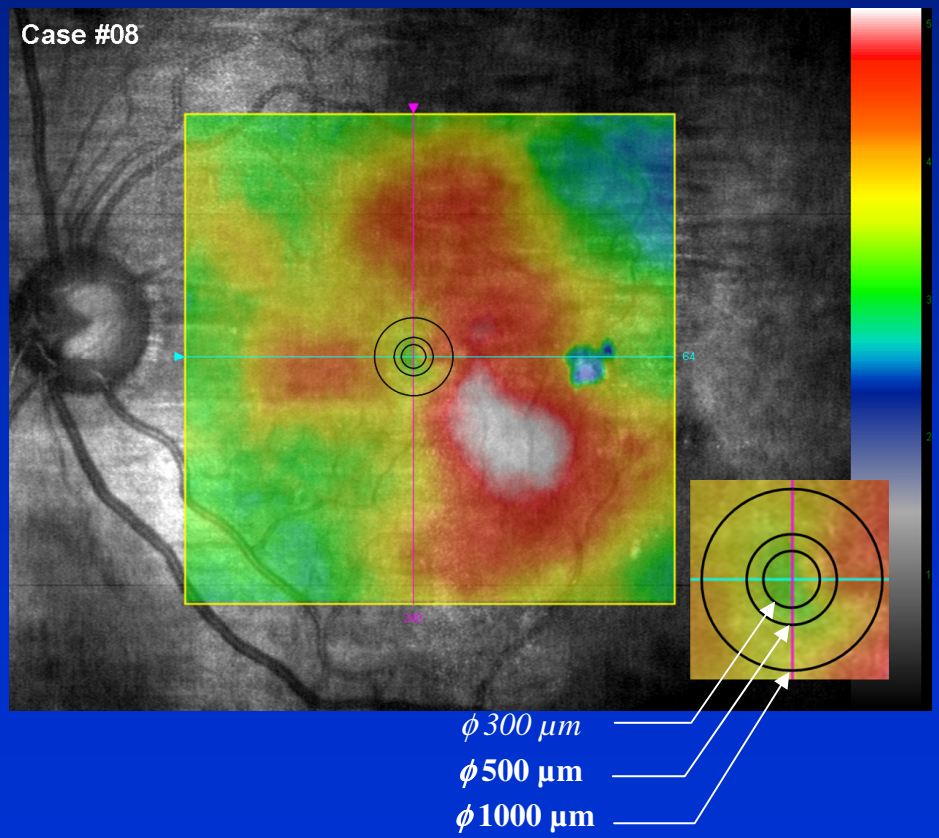
Mapping CSME

With or Without Central Involvement (500 μm)

Fundus Photography

OCT – High Definition

- Spectral Domain



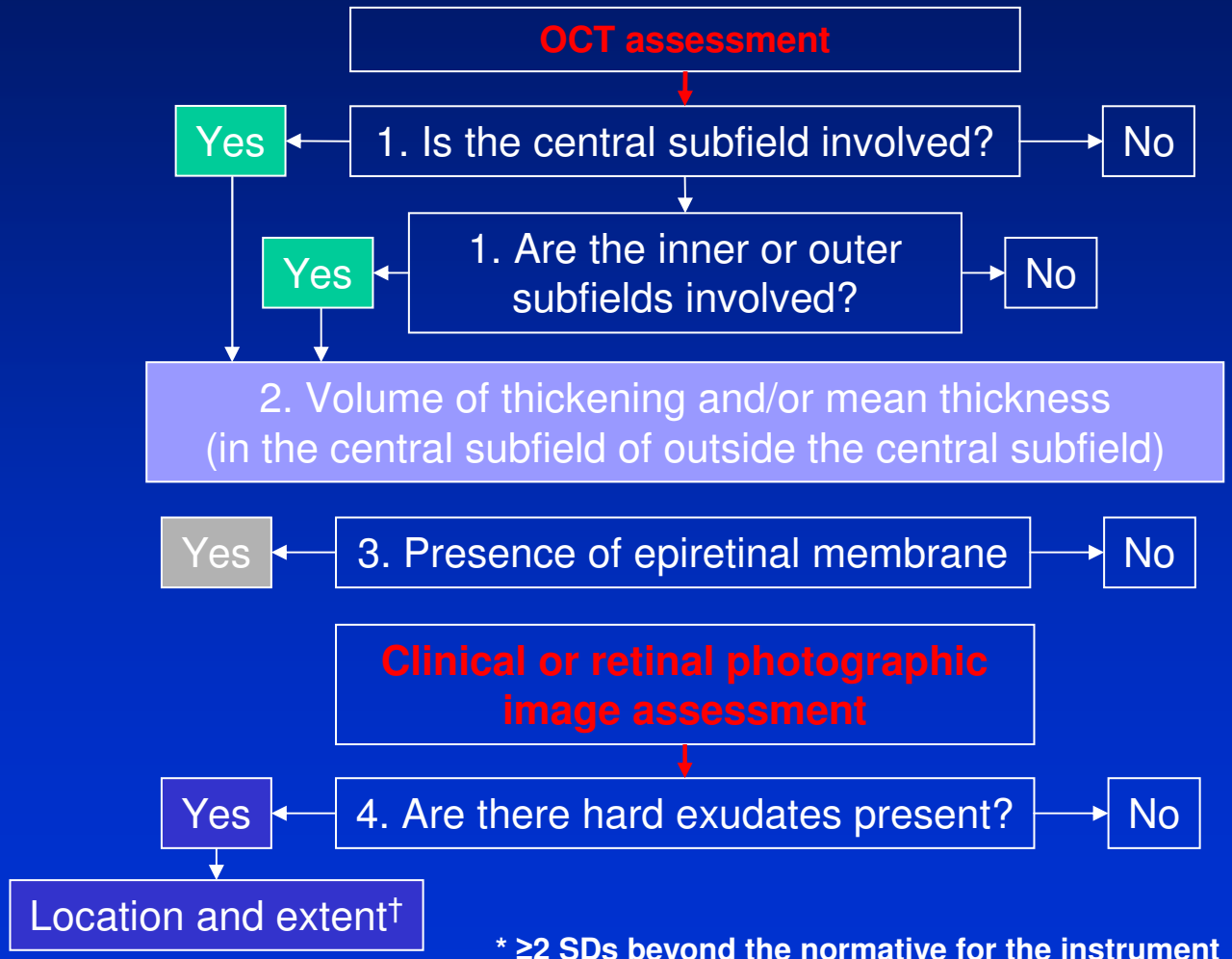
Proposed ME classification

The proposed classification for DME in an individual patient comprises:

1. **Location of edema**
   - Central-involved DME *or*
   - Peri-central inner-involved DME *or*
   - Peri-central outer-involved DME
2. **Amount of edema**
   - Mean thickness, volume and/or logOCT of location **PLUS** total volume of all 9 ETDRS subfields
3. **Vitreoretinal interface abnormalities**
   - Present/absent
     - Epiretinal membrane: present/absent/indeterminate
     - Posterior hyaloid detachment: present/absent/indeterminate
4. **Hard exudates**
   - Present/absent in central subfield

ME classification

1. Location
2. Amount of edema
3. Vitreo-retinal interface abnormalities
4. Hard exudates



* ≥2 SDs beyond the normative for the instrument
† ETDRS/Wisconsin Reading Centre descriptions

2. Frequency – Morbidity

- Diabetic retinopathy (DR) is a major cause of blindness and the primary cause of blindness in working-age individuals in developed countries[1]
- DME is a common manifestation of DR[1,2]
- DME is the main cause of visual impairment in patients with Type 2 diabetes[1,2]
- Although DME does not cause total blindness, it frequently leads to a severe loss of central vision[1]

DME, diabetic macular edema
DR, diabetic retinopathy

1. Simo R and Hernandez C. *Diabetologia* 2008;51:1574–1580.
2. Simo R and Hernandez C. *Diabetes Care* 2009;32:1556–1562.

Epidemiological trends in diabetes and DME

- Prevalence of diabetes expected to approximately double globally between 2000 and 2030[1]
- Number of diabetes cases estimated to reach 300 million worldwide by 2025[2,3]
- Burden of DME likely to increase due to predicted rise in diabetes prevalence[3]
- In the UK, prevalence of DME[4]:
  - Estimated to be 187,842 in 2010
  - Expected to increase to 235,602 in 2020

1. Wild S *et al*. *Diabetes Care* 2004;27:1047–1053.
2. King H *et al*. *Diabetes Care* 1998;21:1414–1431.
3. Chen E *et al*. *CMRO* 2010;26:1587–1597.
4. RNIB and EpiVision. 2009; Future sight loss UK (2): An epidemiological and economic model for sight loss in the decade 2010-2020. Full report http://www.rnib.org.uk/aboutus/Research/reports/2009andearlier/FSUK_2.pdf

Venous Occlusions - Frequency

- Macular Edema - 5-15% BRVO

(over 1 year period)

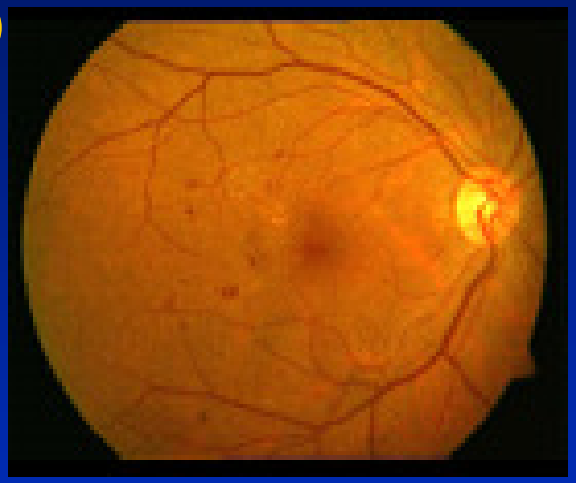
- 18% achieves resolution by 4.5 months
- 41% achieves resolution by 7.5 months

3. Clinical characterization

Diabetic retinopathy: a progressive disease

Nonproliferative DR (NPDR)

- Microaneurysms, intraretinal haemorrhages
- Barrier breakdown (leakage) – exudates
- Capillary closure
- Complication – **DME**

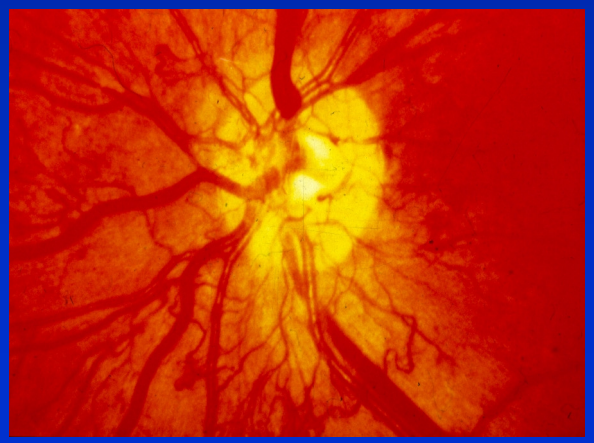


Symptoms

- None
- Vision loss
- Glare

Proliferative DR (PDR)

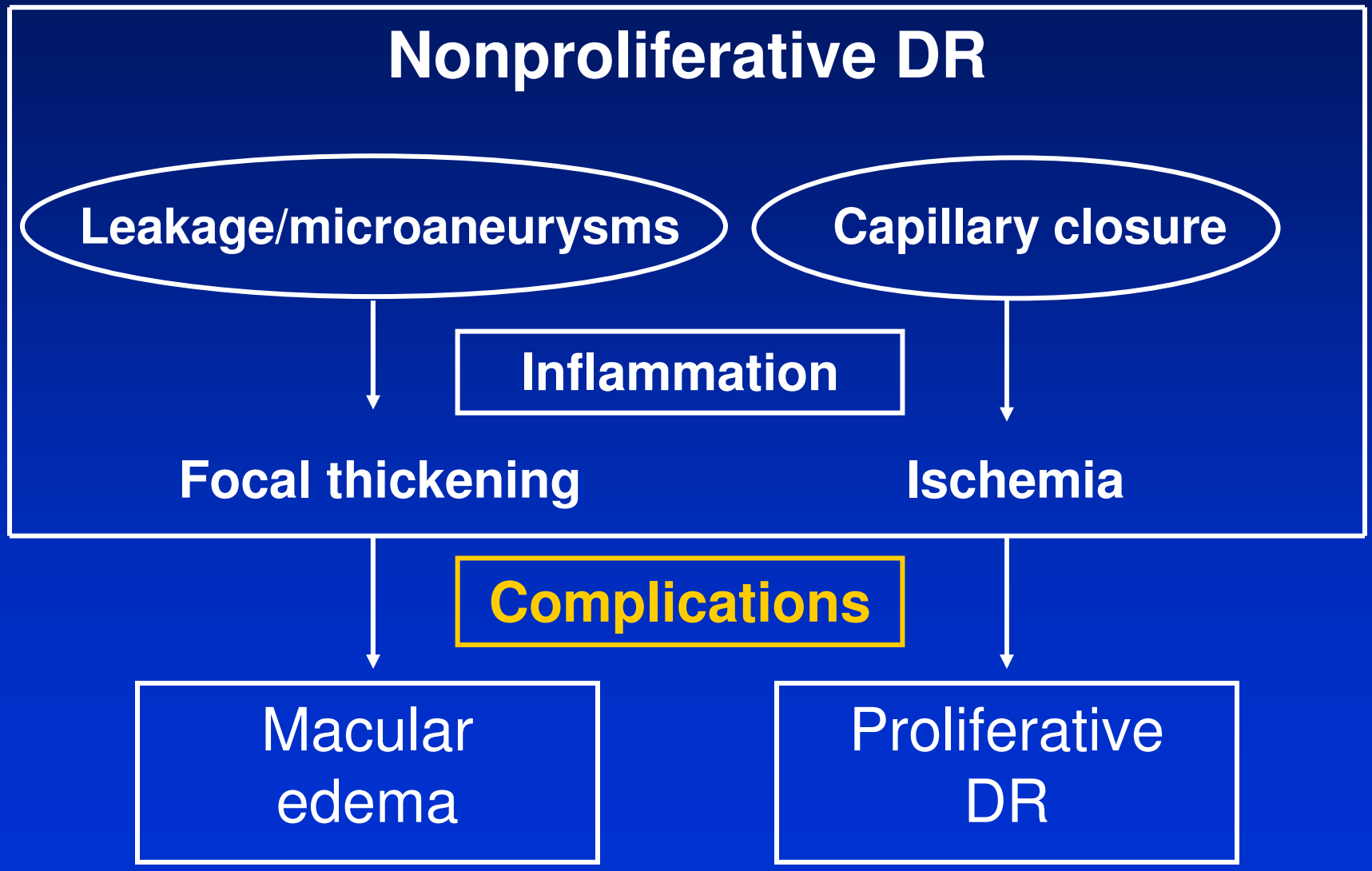
- Neovascularisation
- Vitreous/preretinal haemorrhage



- None
- Vision loss
- Floaters

1. Wilkinson CP *et al. Ophthalmology* 2003;110:1677–1682.
2. Falcão M *et al. Open Circulation and Vascular Journal* 2010;3:30–42.

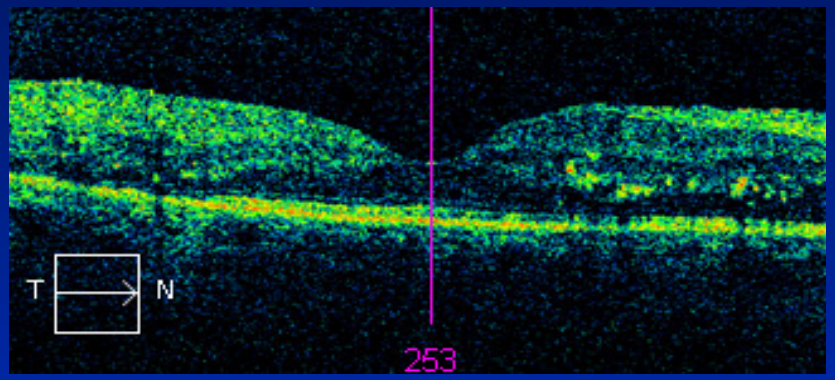
Diabetic retinopathy (DR)



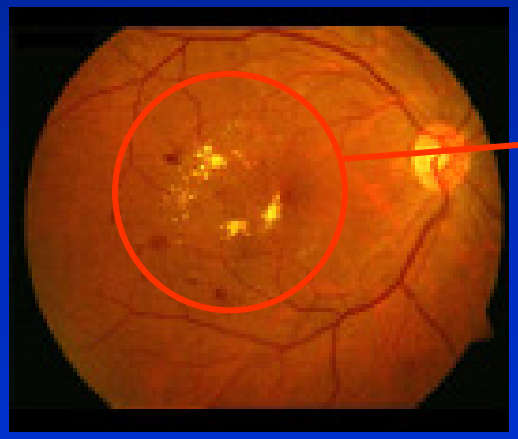
1. Cunha-Vaz J. *Dev Ophthalmol* 2007;39:13–30.

What is Diabetic Macular Edema?

- DME can develop at any stage of DR and is the most common cause of visual loss in nonproliferative DR[1]



- Retinal **thickening** due to accumulation of fluid



- Accumulation of **hard exudates**[2]
- **Microaneurysms** in the central 1000µ

- Severity of DME is based on distance of retinal thickening and/or exudates from the macular centre[2] - **Location to fovea**

1. Lang GE. *Dev Ophthalmol* 2007;39:48–68.
2. Wilkinson CP *et al. Ophthalmology* 2003;110:1677–1682.

Evolution of DR: general clinical impression

- Different evolution in different patients with similar metabolic control
  and duration of disease
- Not all patients develop persistent macular edema
- Not all patients develop neovascularization

NPDR phenotypes: type 2 diabetes

Phenotype A	▪ Slow progression (<2 red dots/year) ▪ Accelerated ageing process (diabetes)
Phenotype B	▪ Rapid progression (>2 red dots/year) ▪ Increased flow ▪ Alterations of BRB – leakage ▪ Increased retinal thickness – edema ▪ Haemodynamic changes predominate
Phenotype C	▪ Rapid progression (>2 red dots/year) ▪ Decreased flow ▪ FAZ outline changes ▪ Thrombotic changes predominate

BRB, blood retinal barrier
FAZ, foveal avascular zone

1. Cunha-Vaz J. *Development Ophthalmology* 2007;39:13–30.

4. Bimomarkers of Progression

Microaneurysm Turnover

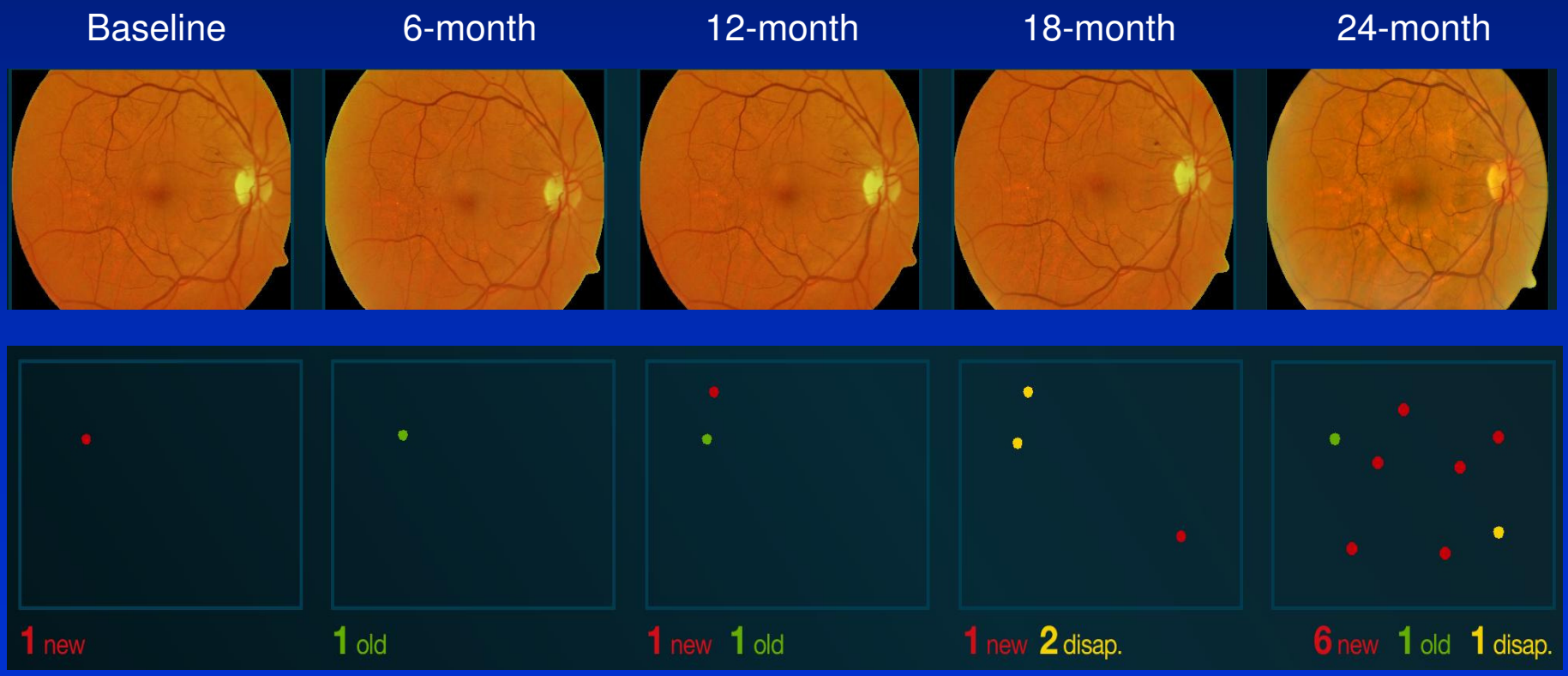
- Evaluation of Progression by counting microaneurysms (red dots) in sequential visits and identifying their exact location in the retina

  – Identifying new microaneurysms (formation rate) – Disease activity + Leakage

  – Identifying disapearing microaneurysm (disapearance rate) – Capillary Closure

Microaneurysm turnover
Methods

MA Turnover - " Retmarker DR "



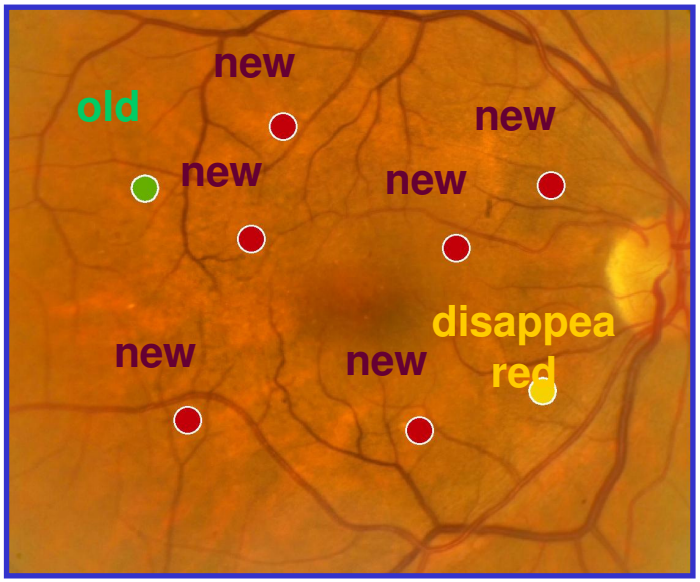
Microaneurysm turnover Methods

MA Turnover - “ Retmarker DR ”

CFP
2-years
follow-up

MA
Earmarking
For each visit

24-month



MA Formation rate of 4 MA/year

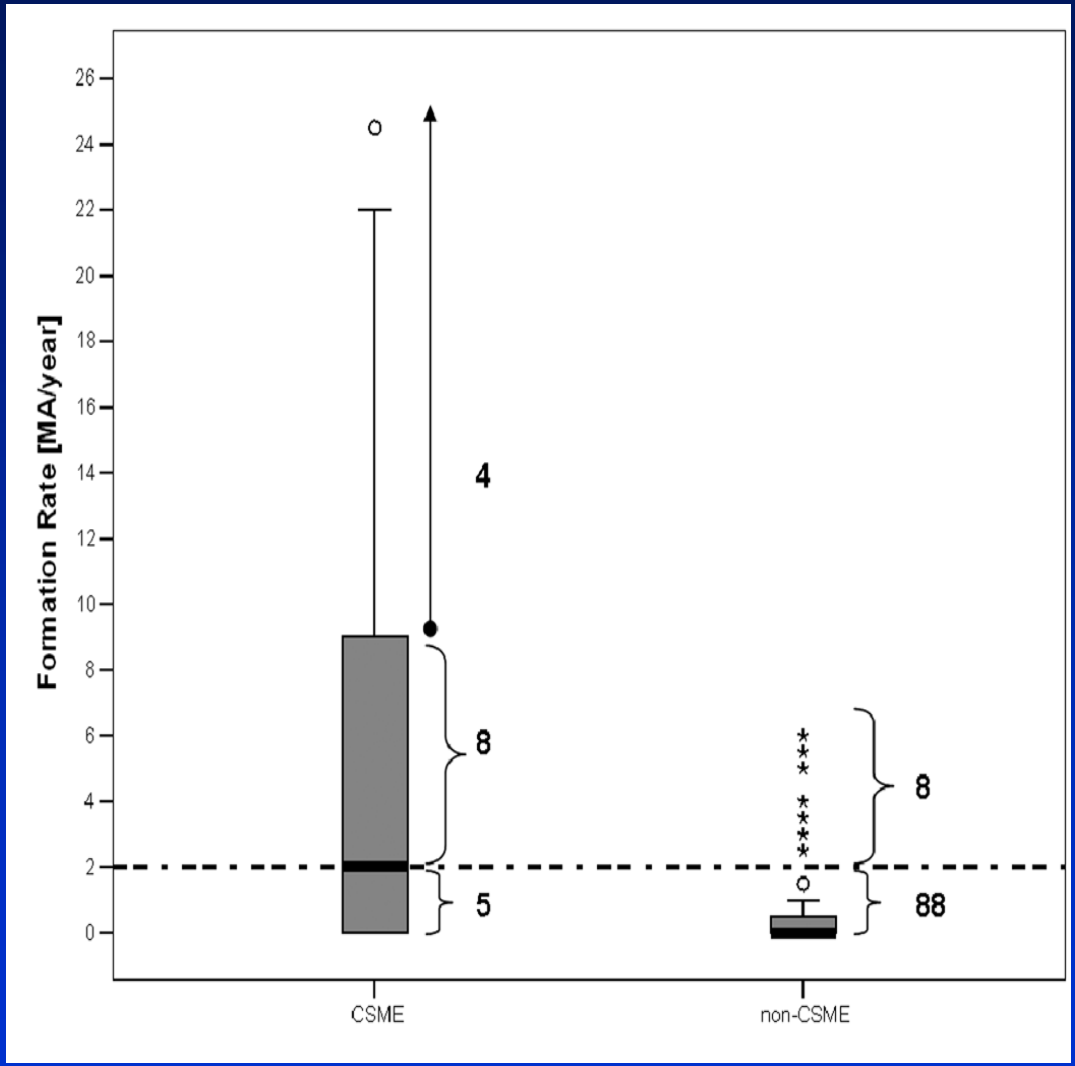
Microaneurysm turnover Results

- **17** patients with **CSME**
(10-Year follow-up of 113 patients)

- **Higher MA turnover**
p<0.001

- **MA turnover ≥ 2 MA/Y**

12/17 (70.6%) vs **8/96** (8,3%)
P=0.002 vs p=0.647



Findings confirmed by Michael Ulbig et al., Munich, Germany.

EVICR.net
(European Vision Institute Clinical Research Network)

- **Network of European certified clinical trial sites (75) from 16 European countries**

- **Centralized infrastructure**

6 Scientific Sections:

⇨ AMD and Retinal Dystrophies
⇨ Diabetic Retinopathy
⇨ Glaucoma
⇨ Cornea, Cataract & Refractive Surgery
⇨ Ocular Surface & Inflammation
⇨ Reading Centres

2. Protocol nº ECR-RET-2010-02

Title: Identifying progression of retinal disease in eyes with NPDR in diabetes type 2 using non-invasive procedures

ClinicalTrials.gov Identifier: NCT01145599

Principal Investigator: J. Cunha-Vaz

Nº Centres involved: 18 (450 patients)

- One year follow-up (0, 3, 6, 12 months)
- Centralized Reading Centre (CORC)

Progression to DME

- Microvascular disease activity - Fundus Photography
  - Microaneurysm Turnover - Retmarker
- Increase in Retina Thickness - OCT
- Association with vision loss (photoreceptors status) - OCT

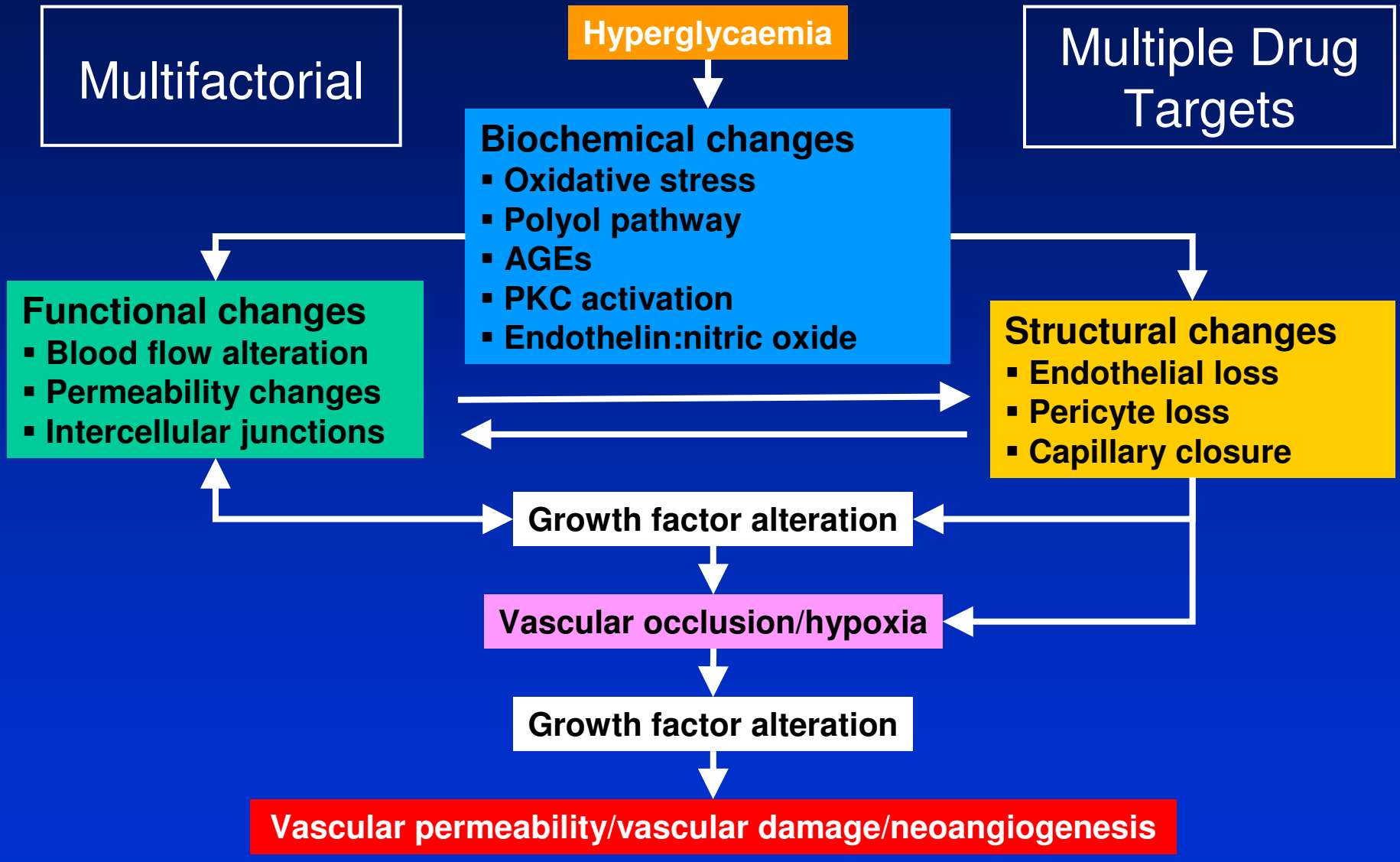
- BCVA -

5. Macular Edema - Pathogenesis

- Breakdown of Blood-Retinal Barrier -

1. Diabetes - Multifactorial changes in the inner BRB
2. Venous Occlusion – Hemodynamic factors
3. Associated role of inflammation and outer BRB

Pathogenesis of diabetic retinopathy



AGE, advanced glycation end-product
PKC, protein kinase C

Adapted from Kahn ZA and Chakrabarti S. *Experimental Diabetes Res* 2003;4:287–301.

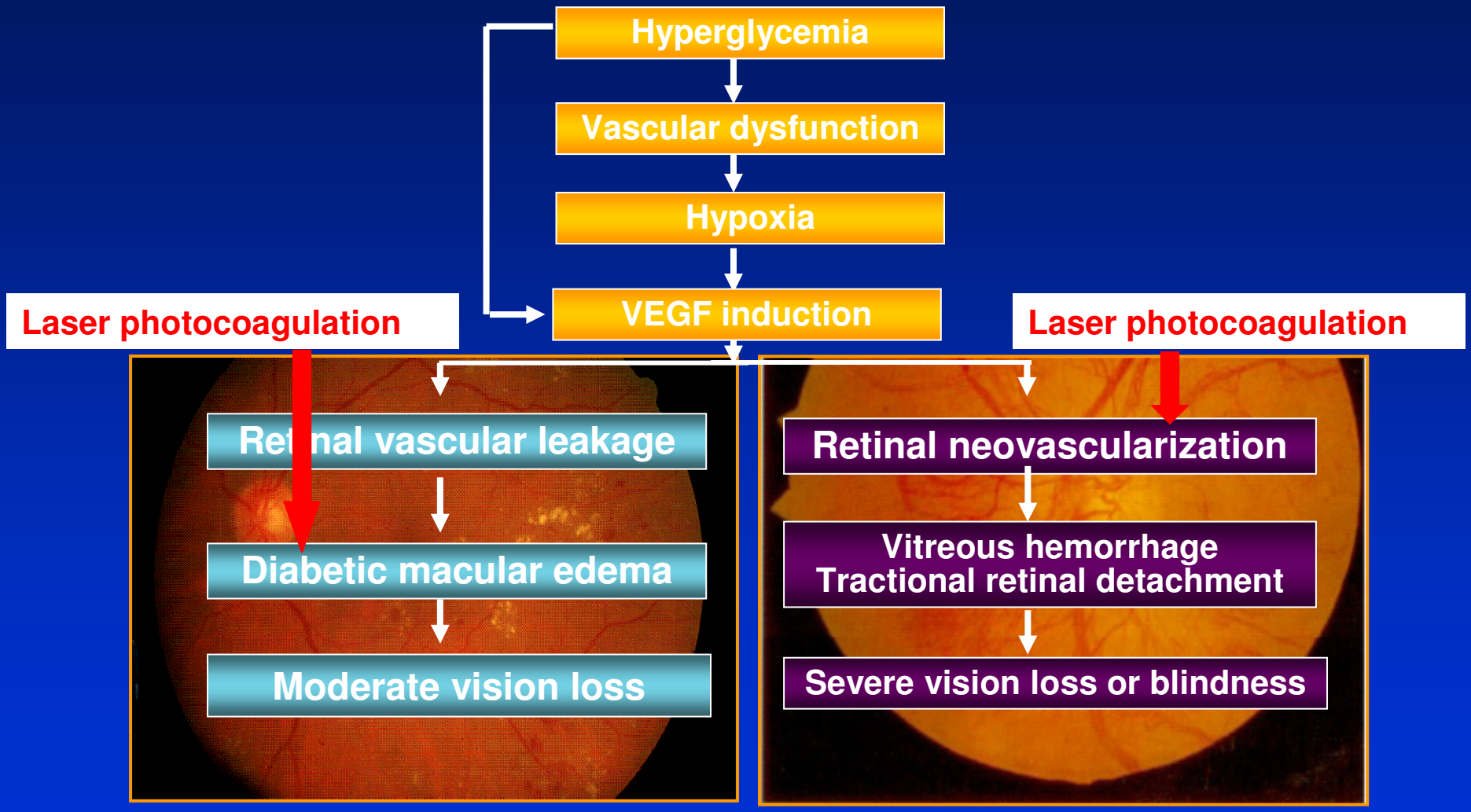
Diabetic Macular Edema – Key points

- DME is a major cause of visual impairment in patients with diabetes
- Burden of DME likely to increase as prevalence of diabetes expected to rise by ~50% globally from 2000 to 2030
- Several biochemical factors and pathways are implicated in the development of DR and DME (complex association to mechanisms)
- VEGF plays a major role in the pathogenesis of DR complications
- The pathogenic profile varies among patients, leading to differing disease characteristics, requiring personalised strategies to manage the disease effectively

6. Treatment of Macular Edema

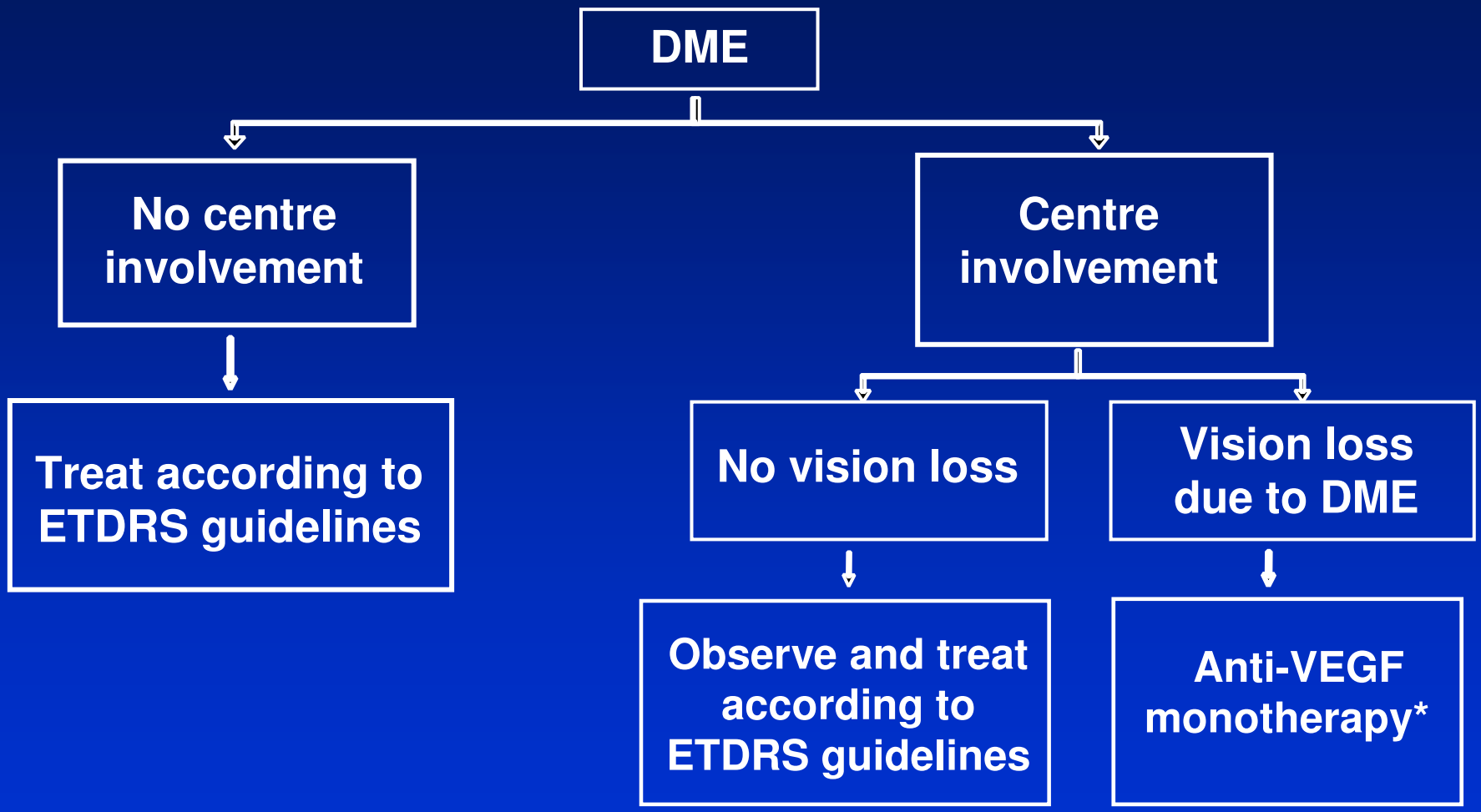
Systemic	Local
Metabolic control	Laser: Conventional vs substreshold
Blood Pressure	Intravit. Antiangiogenics: Lucentis, etc
Lipid Lowering	Intravit. Steroids: Osurdex, Iluvien, etc
	Combination Tx
	Vitrectomy – ILM (?)

Laser Management of DR



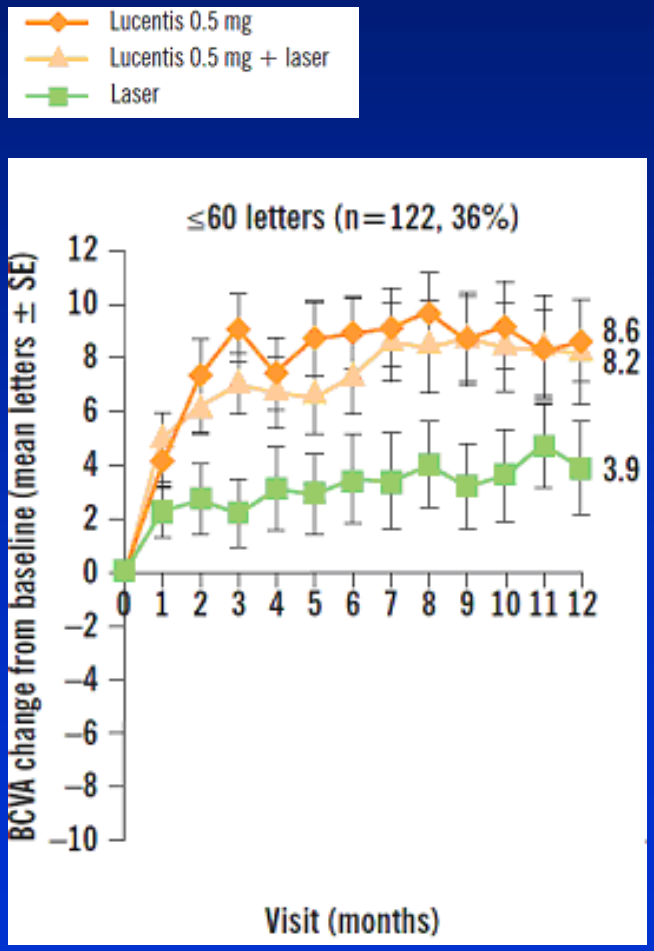
Adapted from Sheetz MJ, King G. JAMA 2002;288:2579-2588.

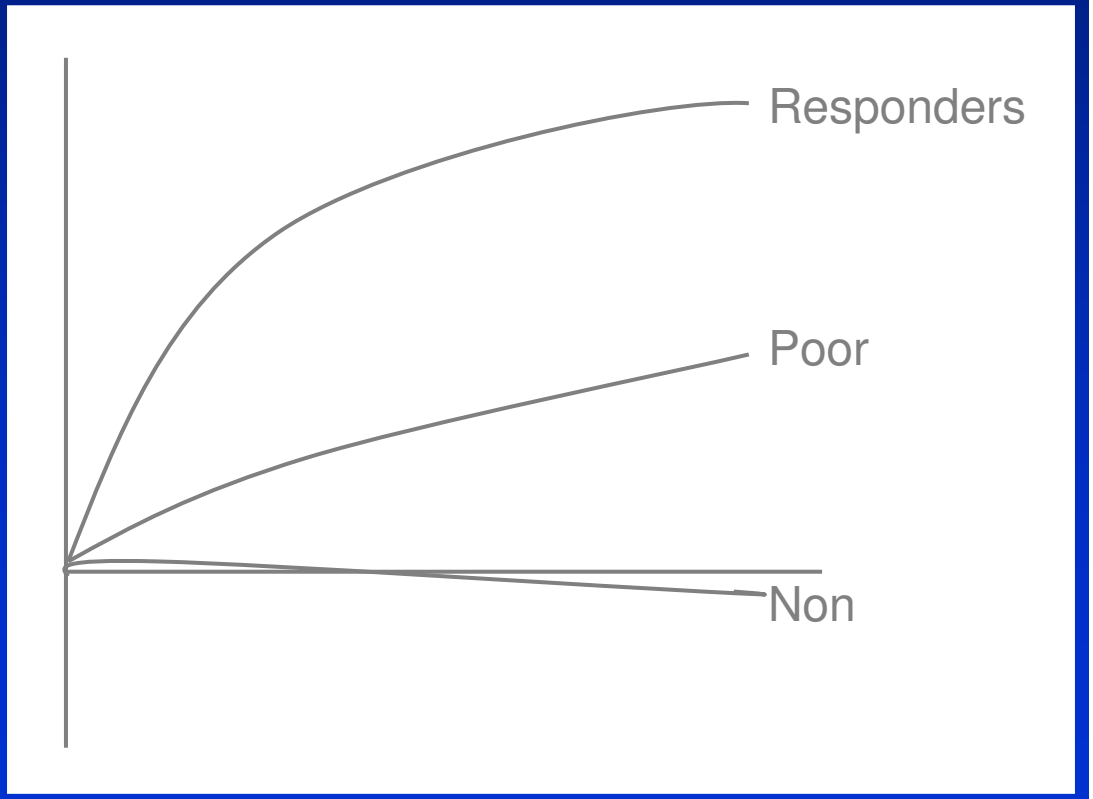
Present view of DME treatment



Different Responders to Anti-VEGF Treatment

Visual Acuity – recovery of photoreceptor function





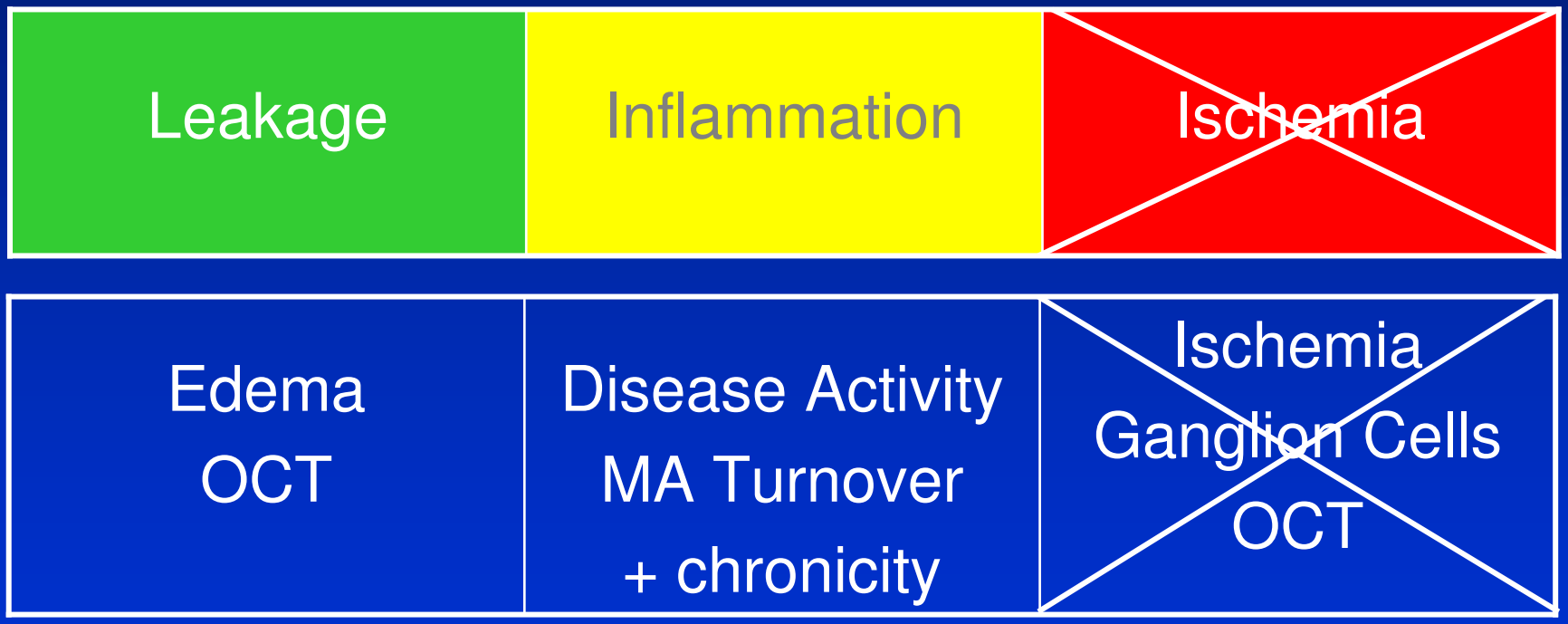
Combination treatments for DME

Anti-VEGF	Loading dose	3-4 injections
Laser	After 1st injection (one week)	

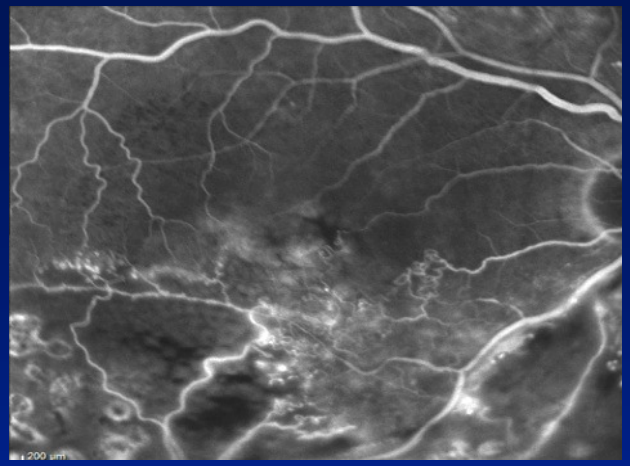
Steroids for non-responders to anti-VEGF treatment

Characterization of Responders

Predominant Disease Mechanism



Treatment Macular Edema in Retinal Vein Occlusions



Macula perfused

- Intravitreal steroids
- Anti-VEGF

Macular ischemia

- Intravitreal steroids
- Anti-VEGF

Neovascularization

Scatter laser to area of ischemia
Consider
- Intravitreal Steroids
- Anti-VEGF

Consensus Management VO. Ophthalmologica 2011,226(4).

Macular Edema Treatment

Depends of response to treatment

Visual Acuity Improvement

Photoreceptors status

Retinal Tickness (Edema)

Leakage intra-retinal fluid

subretinal fluid (VA)

Macular Edema

1. Definition based on OCT (non-invasive, objective)
2. Increasing frequency
3. Different patients - Different rates of progression
4. Microaneurysm Turnover - Biomarker in diabetes
5. Pathogenesis – Complex/Alt of Blood-Retinal Barrier
6. Treatment of Macular Edema – Personalized / Response to Tx

→ Combination Therapy